Infectious Disease Update

Vanderbilt Transplant Advanced Practice Provider Symposium
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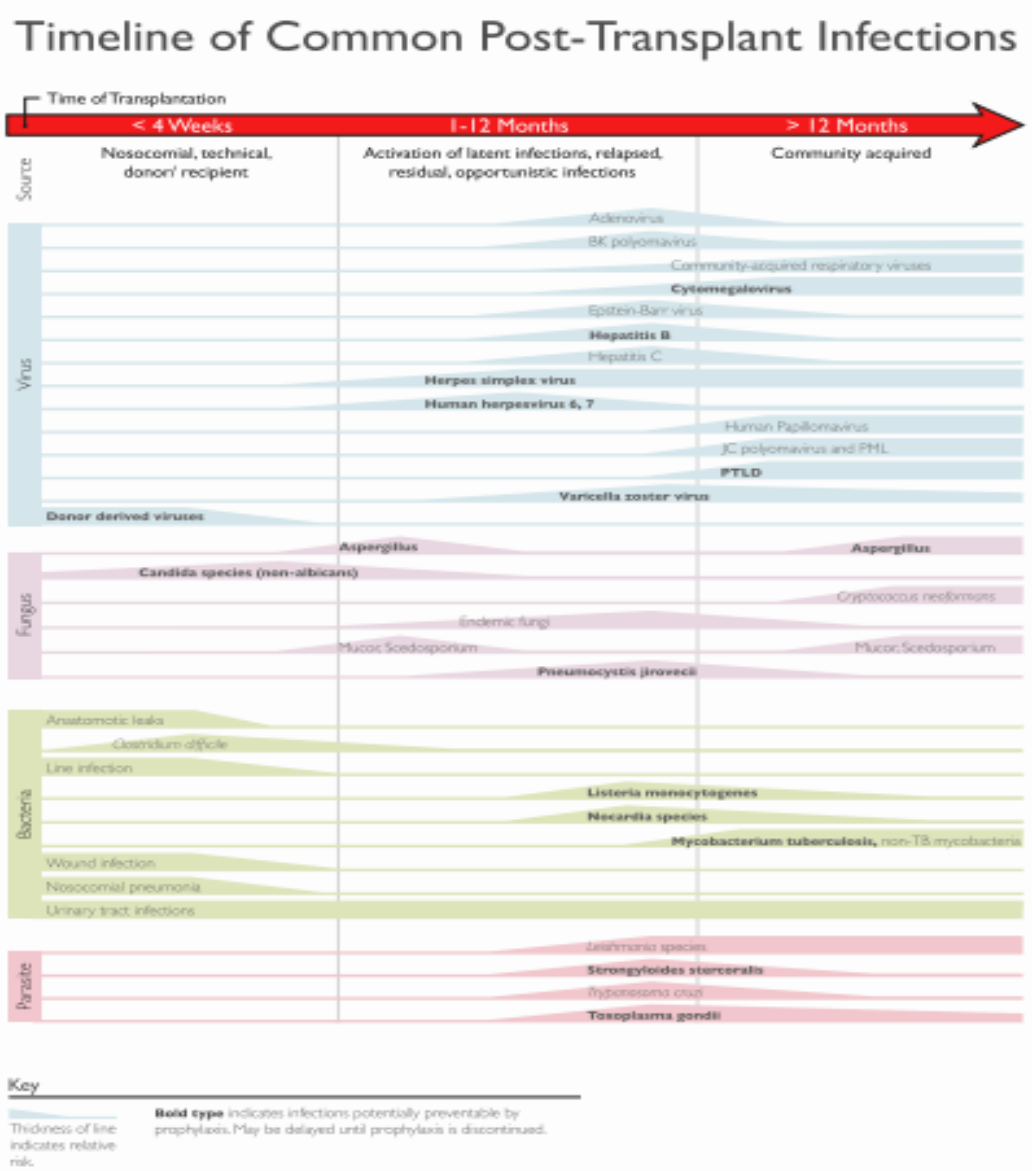
What are common infections and when should we have suspicions for them?



Fishman, J.A. American Journal of Transplantation, Volume 17, Issue 4, 856 - 879

Infections <4 weeks: Nosocomial, Technical, Donor/Recipient

Urinary Tract Infections

Terminology

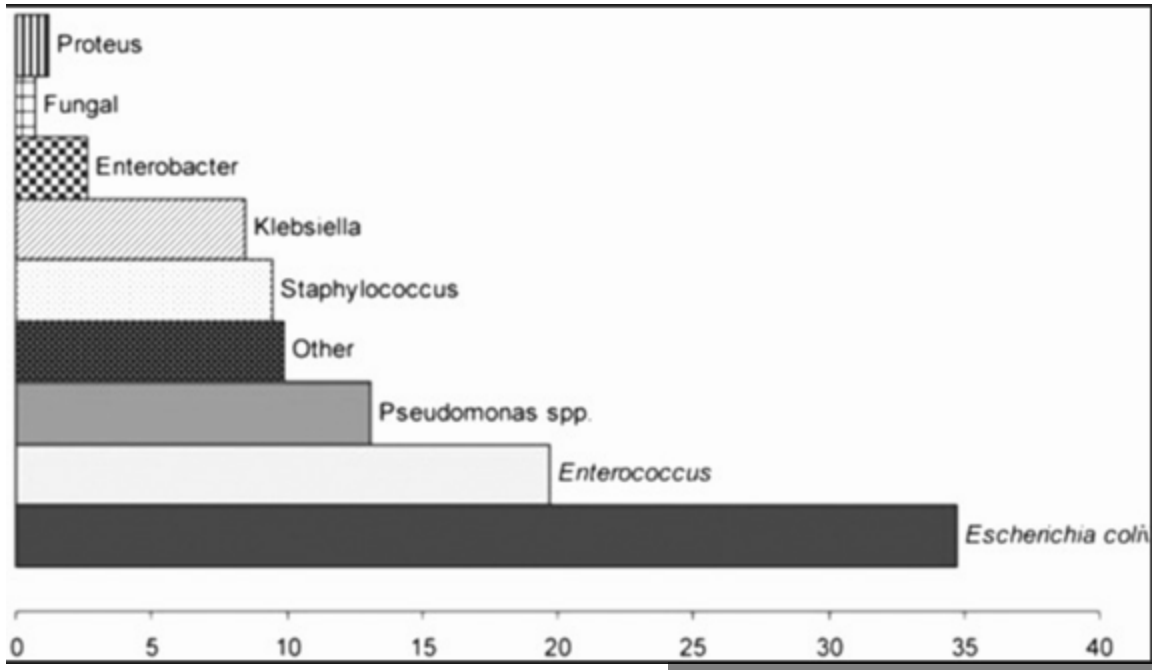
- Asymptomatic bacteriuria
  - Presence of bacteria on urine culture with no local or systemic symptoms.
- Simple cystitis
  - Presence of bacteria on urine culture with local urinary symptoms, such as dysuria, frequency, or urgency, but no systemic symptoms, such as fever, allograft pain and no indwelling device (ureteral stent, nephrostomy tube, or catheter).
- Complicated UTI
  - Presence of bacteria on urine culture with fever, allograft pain, chills, malaise, or bacteremia with the same organism in urine, or a biopsy consistent with pyelonephritis.
- Recurrent UTI
  - Two or more episodes of UTI in 6 months, or 3+ episodes of UTI in one year.

Risk Factors for UTI

- Female sex
- Advanced age
- Recurrent UTI prior to transplant*
- Vesicoureteral reflux
- Urethral catheterization
- Ureteral stent placement
- Deceased donor kidney transplant
- History of PCKD
- Delayed graft (kidney) function

What organisms do we suspect?

- Gram negative organisms (56-90%)
  - E. coli (most common)
  - Pseudomonas aeruginosa
  - Enterobacter cloacae
  - Klebsiella pneumoniae
  - Klebsiella oxytoca



Parasuraman & Julian, 2013

Management of Symptomatic Infections

Initial selection of antibiotics is based upon knowledge of local antibiotic resistance patterns and the patient's history of past causative organisms and antibiotic exposure.

Definitive treatment is administered once the species and antibiotic susceptibilities of the micro-organism are identified.

Empiric antibiotic selection for simple cystitis

- Preferred oral agents for empiric therapy of simple cystitis in transplant recipients include:
  - PO fluoroquinolone (ciprofloxacin and levofloxacin, renally dosed)
  - Third generation cephalosporin (cefdinir and cefpodoxime)
  - Amoxicillin-clavulanate

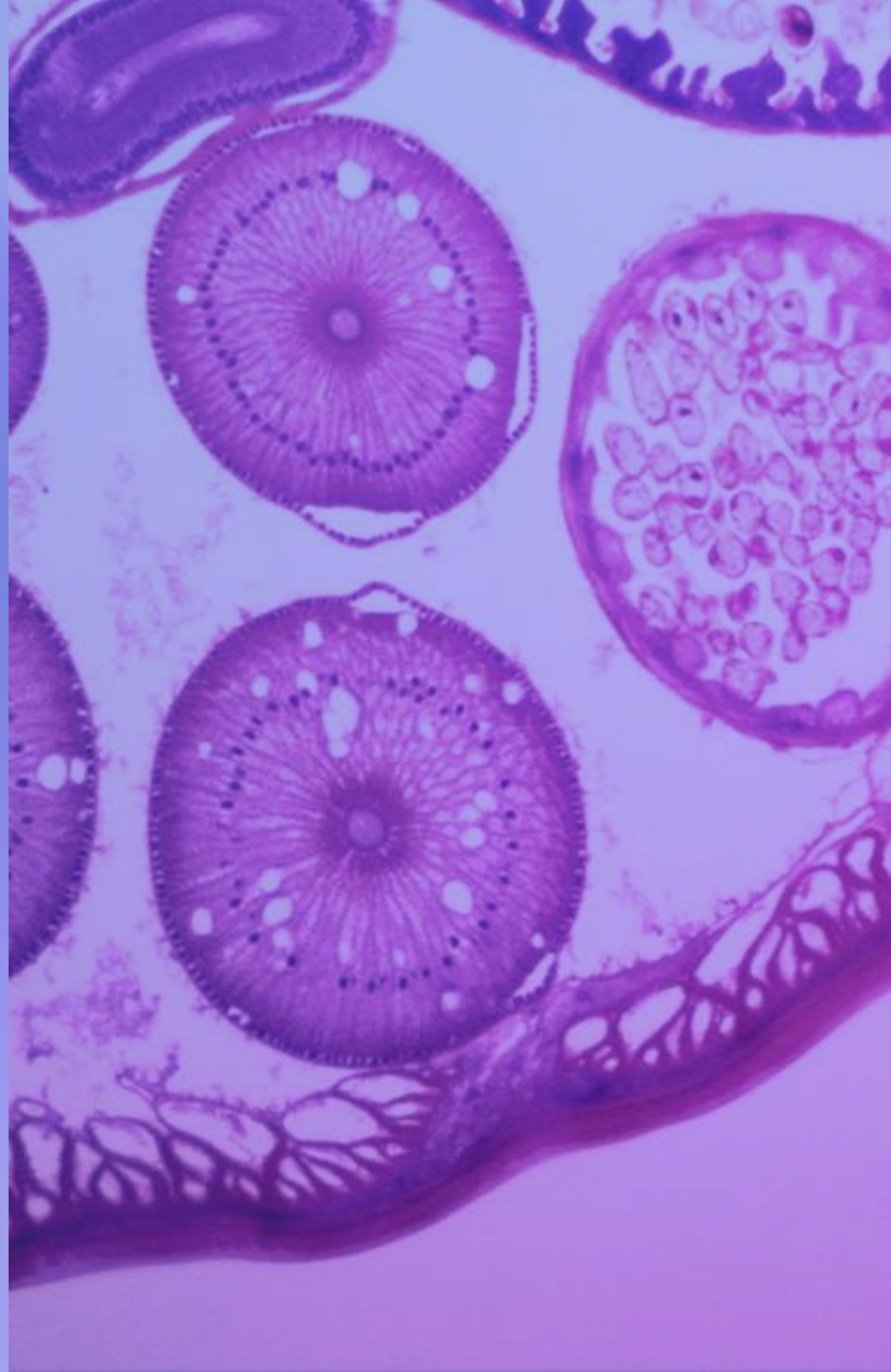
  - Take into consideration patients **most** recent prior culture results. Ideally for empiric treatment, pick drug that was sensitive previously.

Lesser empiric antibiotic choices for simple cystitis

- Nitrofurantoin is an option *for patients with GFR >30*
- Fosfomycin and TMP/SMX should not be routinely used for empiric therapy in transplant recipients. Transplant patients who have recently been on TMP/SMX (eg, for prophylaxis) should be assumed to be infected with an organism that is resistant to TMP/SMX.

Complicated UTI/Pyelonephritis

- Typically, empiric treatment involves IV antibiotics that cover both gram positive and gram-negative bacteria.
- Empiric antibiotics should have adequate coverage against P. aeruginosa, enteric gram-negative organisms, and enterococcus species.
  - Ceftriaxone
  - Piperacillin-tazobactam
  - Meropenem (history of MDRO)
  - Combination therapy with vancomycin + cefepime



Reducing Risk Factors of UTI immediate post-operatively post-transplant

- Early ureteral stent removal in post-kidney transplant recipients (<4 weeks ideal)
- Timing of ureteral foley catheter removal
- Hygiene

Monitoring for Asymptomatic Bacteriuria

- The IDSA recommends against screening for or treating asymptomatic bacteriuria.
- Monitoring for asymptomatic bacteriuria after 2 months posttransplant has not been shown to be effective in preventing symptomatic UTI, pyelonephritis, blood stream infection, or allograft rejection and can lead to unnecessary antibiotic administration.

Nicolle et al., 2019

Urinary Tract Infection Recurrence

- Why do patients get recurrent UTIs?
  - Anatomic issues
    - Strictures, stones, BPH, functional syndromes
  - Instrumentation
    - SIC, chronic foley
  - Post-coital
  - Noninfectious causes
    - Vaginal atrophy
  - Prostatic involvement

Urinary Tract Infection Recurrence Work-Up

Imaging:

- Renal US, CT a/p, prostate US assessing for prostatitis, fluid collections, stones

Post void residuals

STI w/u

Hygiene

Urology and possibly GYN evaluation

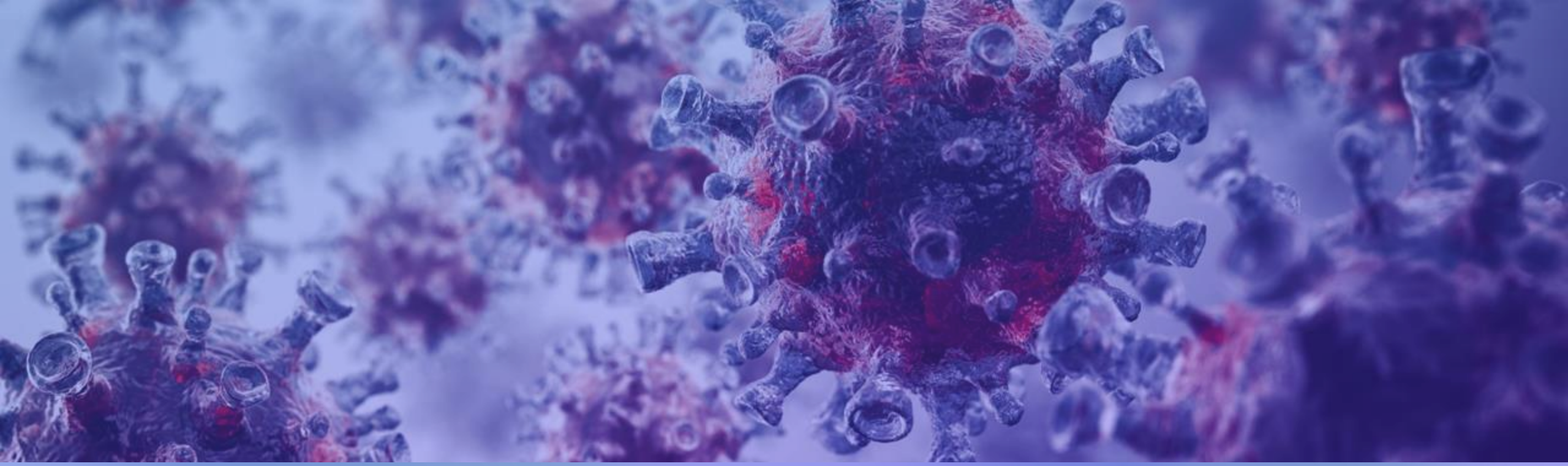
Urinary Tract Infection Recurrence Treatment Strategies

Non-antibiotics:

- Methenamine
  - AVOID if patient also on bactrim.
- Ellura, cranberry extract.

Antibiotics:

- Utilized when the above can't be used or ineffective.



Infections 1-12 Months: Activation of latent infections and opportunistic infections

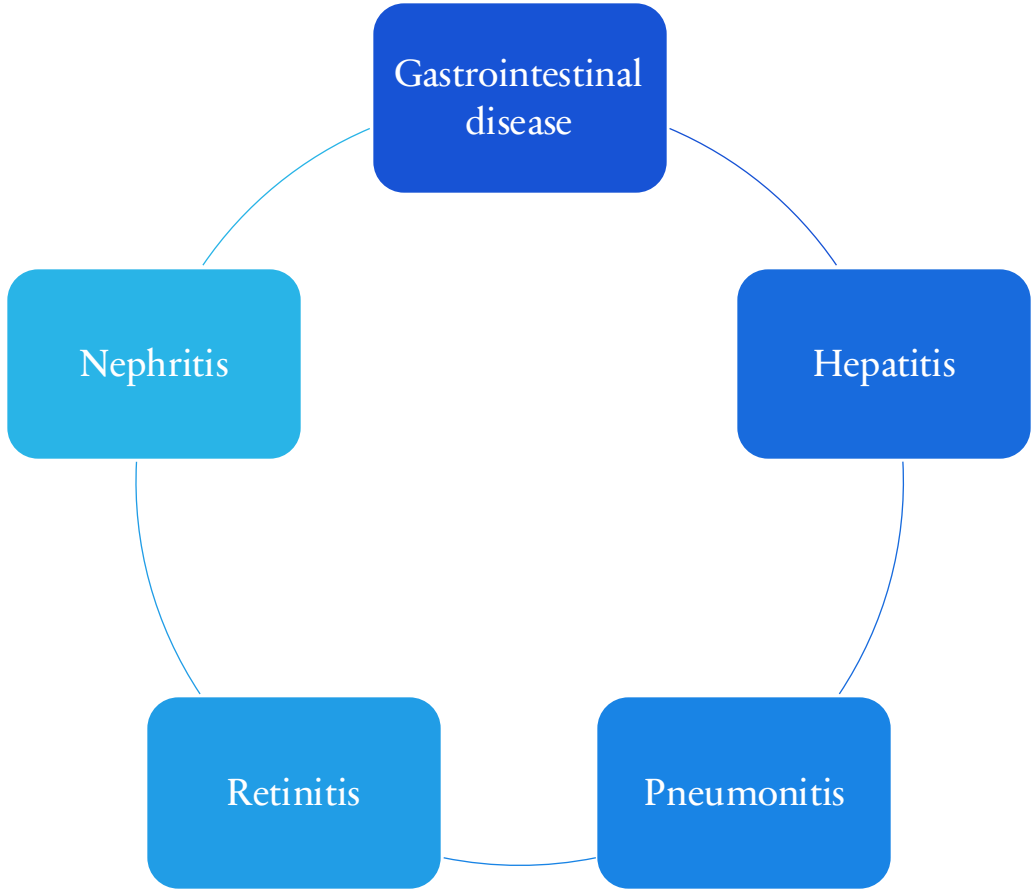
Cytomegalovirus

Herpesviruses

CMV General Principles

- **CMV infection** --> presence of CMV replication in blood regardless of wether signs or symptoms are present
- **CMV syndrome** --> presence of detectable CMV in blood associated with clinical manifestations **without** end organ damage
- **CMV end organ disease** --> presence of detectable CMV in blood associated with clinical manifestations with end organ damage

CMV end organ damage



Why do we care so much about CMV?

- **CMV disease** can be associated with :
  - acute and chronic rejection
  - arteriosclerosis and cardiovascular disease
  - opportunistic infections
  - End organ disease
- **Prevention of CMV** is crucial to avoid both direct and indirect effects and optimize transplant outcomes.

SOT Patients at risk

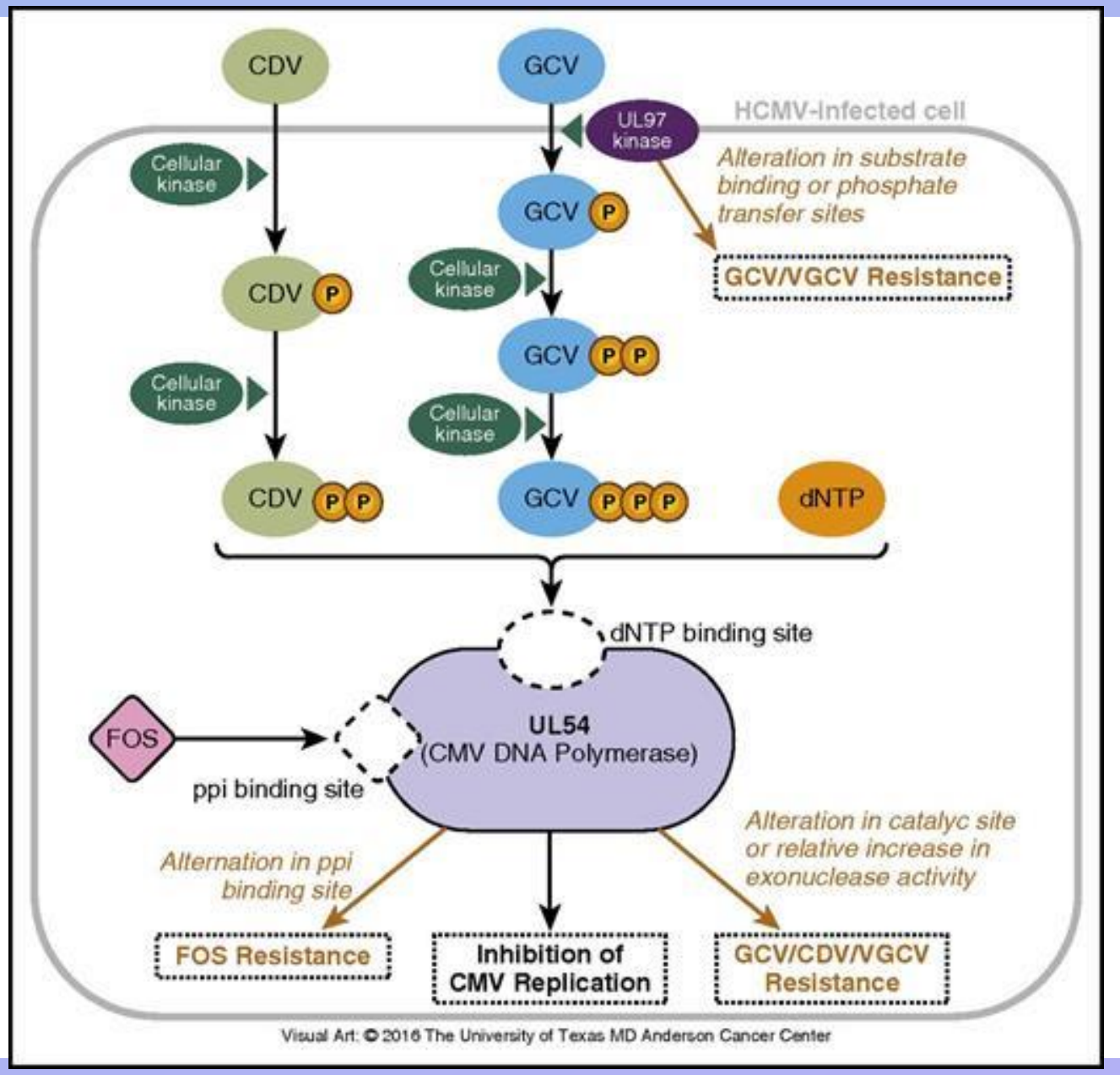
- Primary infection: D+/R-
- Reactivation in D-/R+ and D+/R+
- Increased immunosuppression
- Immediately after completing primary prophylaxis

Complications

- **Refractory CMV infection**: CMV DNAemia with >1log10 increase on viral load after at least 2 weeks of appropriately-dosed antiviral
- **Resistant CMV**: Genetic alteration causing reduced susceptibility to antivirals

Causes of CMV Resistance

- High state of immunosuppression
  - T-cell depleting therapy
  - Lack of CMV immunity
- Subtherapeutic antiviral level
  - Appropriate dosing
  - Absorption
  - Compliance
- Genetic resistance


CDV
GCV
HCMV-Infected cell
UL97 kinase
Alteration in substrate binding or phosphate transfer sites
Cellular kinase
GCV P
GCV/VGCV Resistance
CDV P
Cellular kinase
GCV P P
Cellular kinase
Cellular kinase
CDV P P
GCV P P P
dNTP
dNTP binding site
FOS
UL54
(CMV DNA Polymerase)
ppi binding site
Alteration in catalyc site or relative increase in exonuclease activity
Alternation in ppi binding site
FOS Resistance
Inhibition of CMV Replication
GCV/CDV/VGCV Resistance
Visual Art: © 2016 The University of Texas MD Anderson Cancer Center

Commonly Used Antivirals

Drug	Use	Toxicity
Valganciclovir	Prophylaxis, Treatment	Leukopenia
Ganciclovir (IV)	Prophylaxis, Treatment	Leukopenia
Foscarnet (IV)	Treatment	Nephrotoxicity
Maribavir	Treatment	Dysgeusia, GI intolerance
Letermovir	Prophylaxis	GI intolerance

Adoptive CMV T-cell Therapy

- Limited availability (participating centers)
- No large RCT
- ? Clinical efficacy and long-term outcomes

Reduction of immunosuppression is a key part of treatment!

Herpes Simplex Virus

Disease	Presentation	Treatment
Mucocutaneous disease	Painful orolabial, genital lesions	Acyclovir (IV, PO) Valacyclovir Famciclovir
Severe, visceral, disseminated	Esophagitis, hepatitis, pneumonitis	IV acyclovir
HSV keratitis	Infection of the cornea	Topical ganciclovir, acyclovir PO acyclovir, valacyclovir, famciclovir

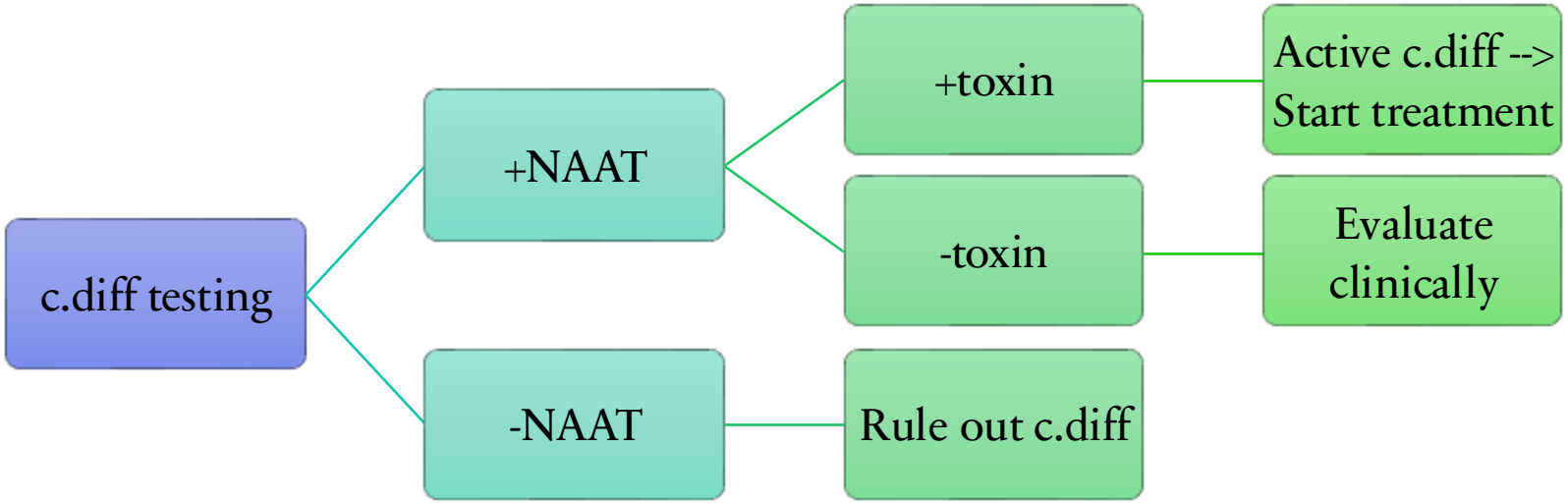
- **Diagnosis**: PCR of lesions and CSF
- Serology is useful to guide post-transplant risk, but it is not sensitive to diagnose acute infection (false positive IgM)

HSV Treatment

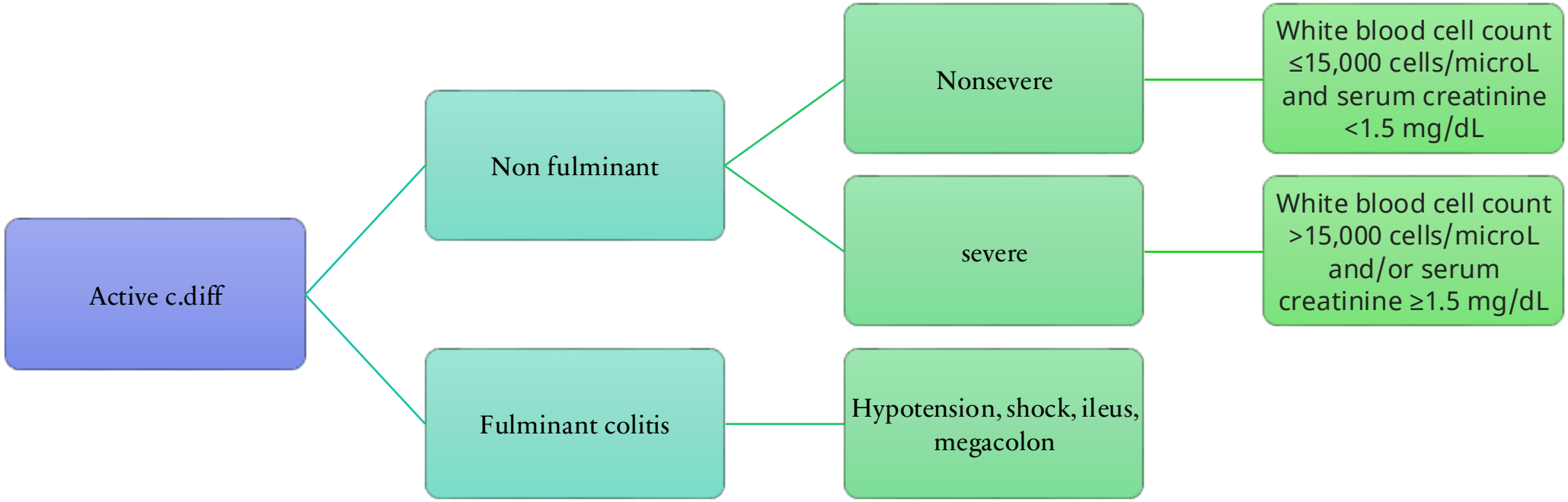
- Acyclovir (PO, IV): up to 3x/day
- Valacylovir (PO): up to 2x/day
- Famciclovir (PO): up to 2x/day
- Foscarnet, Cidofovir (IV) are reserved for acyclovir-resistant HSV

- IV acyclovir has high nephrotoxicity risk and is challenging to start outpatient

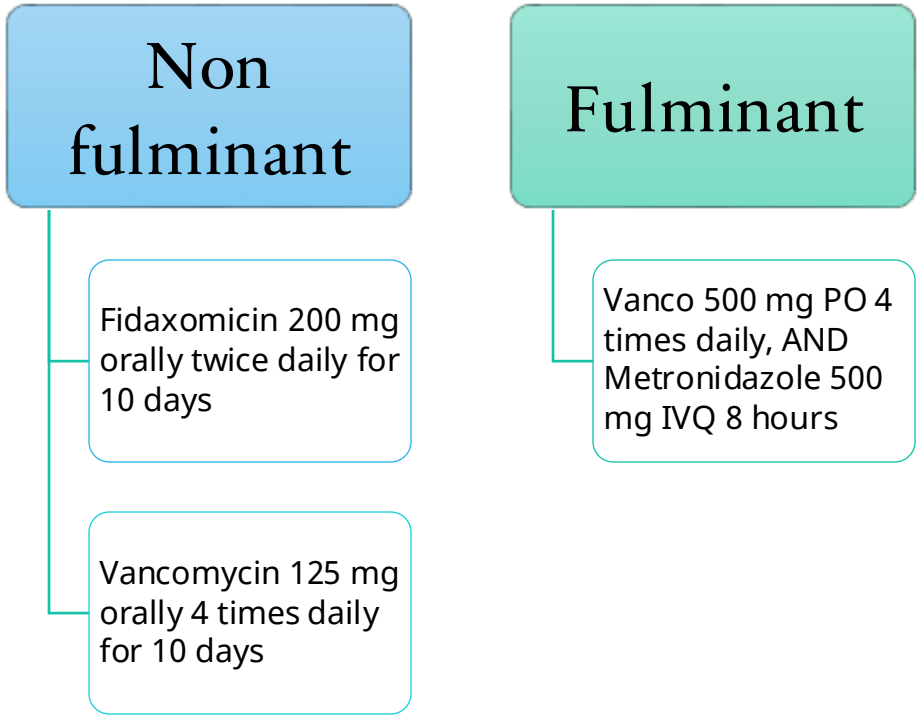
C. diff - Diagnosis



C.diff - Severity



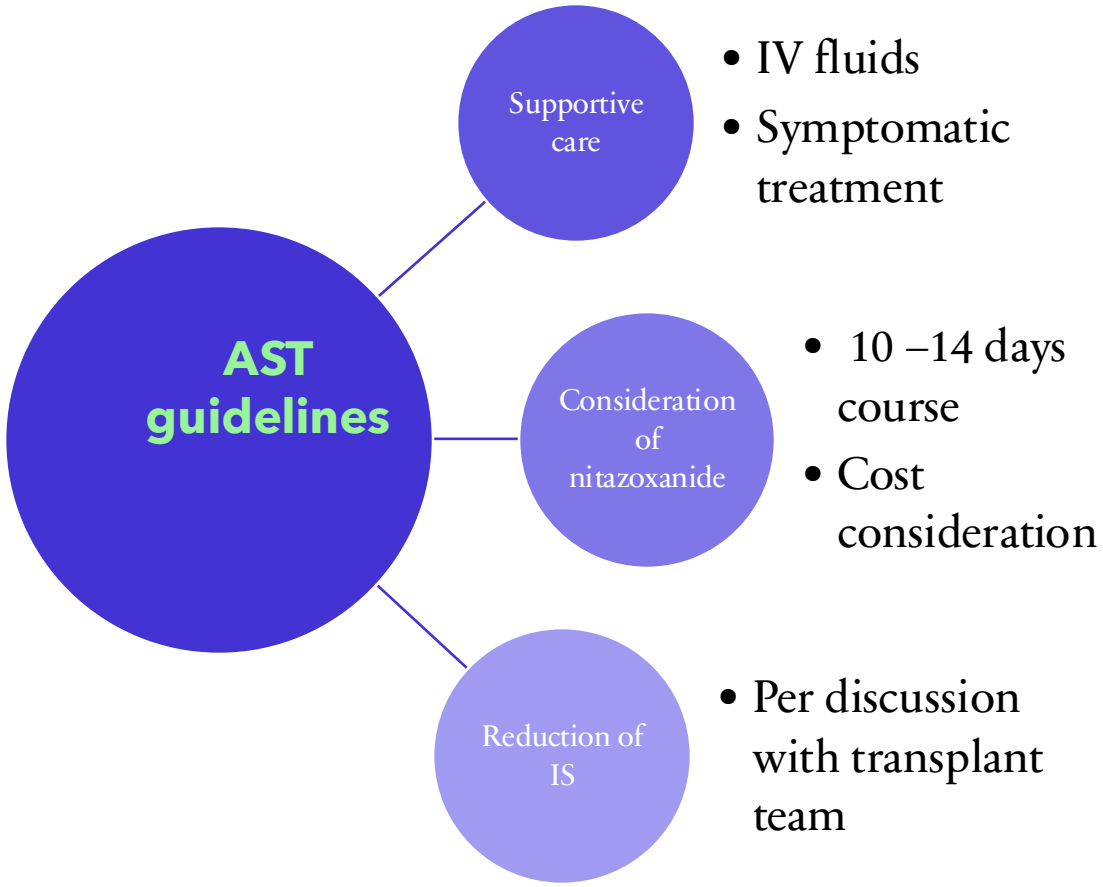
C.diff - Treatment

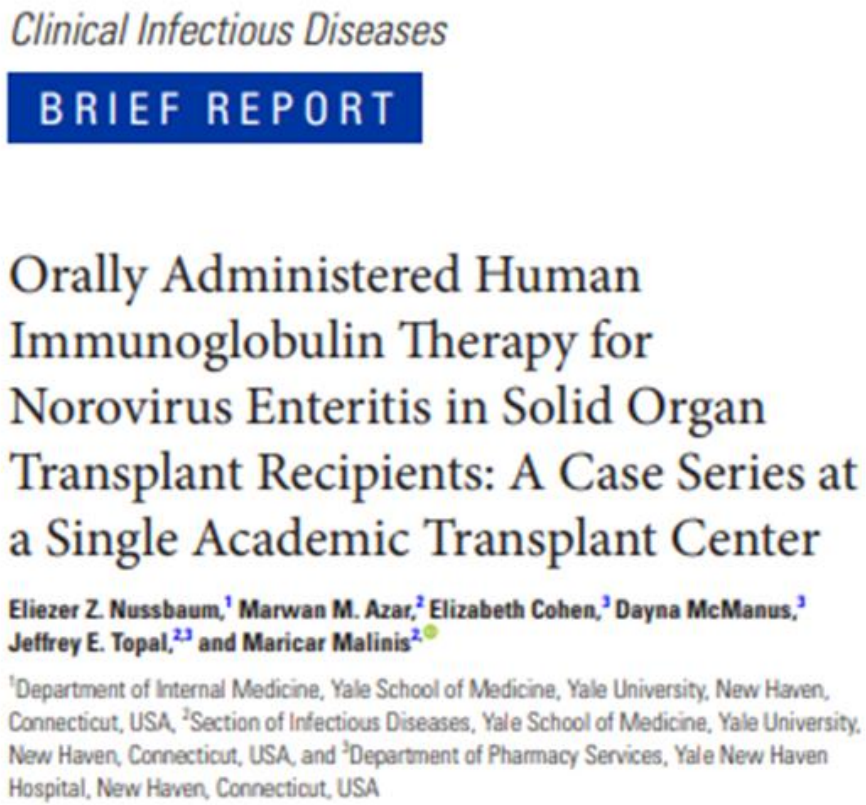


- For **recurrent episodes**, longer courses of fidaxomycin or vancomycin PO with taper
- **Fidaxomycin** preferred over PO vancomycin given a small benefit with respect to recurrence rates
- **Bezlotuxumab**, a monoclonal antibody that binds to toxin B, can be used as a one time infusion for recurrent episodes. Given with standard of care it can decrease the rate of recurrent disease.

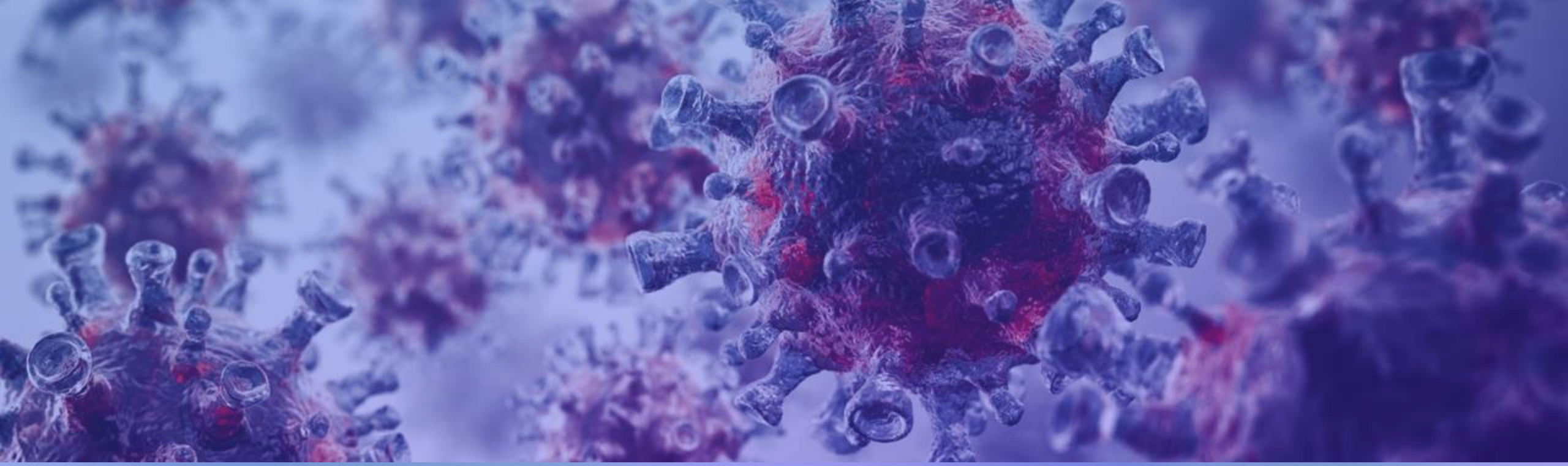
Norovirus/sapovirus

- **Norovirus** is the most common viral cause of gastroenteritis worldwide
- **Patient presentation :** multiple episodes of diarrhea per day, with N/V + positive GI panel





- Treatment was administered in the form of 10 mL of 15%–18% **human immunoglobulin** given **orally** every 6 hours for 8 doses
- Treatment with **OHIG** was associated with an immediate clinical response within days of treatment and with complete and sustained resolution of diarrhea in the majority of patients.
- **How does it work?** Hypothesized to involve binding of viral particles to passively transferred immunoglobulins in the digestive tract, thus inhibiting adherence to complex carbohydrate receptors on the intestinal epithelium + IG induced increases in anti-inflammatory cytokines and reduced proinflammatory cytokines
- **Why not IV?** OHIG is able to achieve higher intestinal concentration than IVIG and several studies have shown that oral immunoglobulins are able to resist proteolytic digestion in the gastrointestinal tract



Infections >12 months: Community acquired

Non-tuberculous mycobacteria overview

Non-Tuberculous Mycobacteria (NTM) Infections

- There are **>100** NTM species that cause infections. Most common among SOT is ***M. avium complex* (MAC)**, specifically *M. avium* and *M. intracellulare*
- Most common manifestation is **pulmonary** infection, but presentation depends on the species and can be disseminated
- Can be found as environmental **contaminants** causing lung colonization
- NTM subspecies have **different drug susceptibilities**

Treatment Challenges

- Treatment regimen usually involves 3-4 drugs
- Significant drug toxicities
- Significant drug interactions
  - Rifampin: ↓ tacrolimus, cyclosporine, sirolimus
  - Macrolides: ↑ tacrolimus, cyclosporine, sirolimus
- Treatment is long, usually up to 12 months

Establishing correct diagnosis and obtaining NTM susceptibilities are **crucial**!

NTM Diagnostic Criteria

- **Clinical and Radiologic criteria** (ALL required)
  - Relevant symptoms
  - Relevant imaging findings (nodular or cavitary lesions)
- **Microbiologic criteria** (at least 1)
  - At least 2 positive sputum cultures
  - At least 1 positive BAL culture
  - Biopsy showing mycobacterial features

Griffith et al. ATS/IDSA Guidelines on Nontuberculous Mycobacterial Diseases. 2006

How to protect our patients beyond transplantation?

Why vaccinate prior to transplant?

- Increased risk of infectious complications post-transplant
- Vaccine response is diminished in organ failure, transplant candidates should be immunized early in the course of their disease
- Live vaccines are **NOT** administered post-transplant (MMR and varicella).

Recommended Vaccinations

- Influenza
- COVID (primary + boosters)
- RSV (>60 yo)
- PCV20
- Gardasil (<45yo)
- Hepatitis A (2 doses: expedited administration is 0d, 6mo)
- Hepatitis B (2 doses: expedited administration is 0d, 1mo)
- Shingrix (2 doses: expedited administration is 0d, 1-2mo)
- MMR (**LIVE**, cannot transplant <4 weeks prior to administration)
- Varicella (**LIVE**, cannot transplant <4 weeks prior to administration)

Post-Transplant Vaccinations

- Inactivated vaccine can be administered starting at 3-6 months post-txp once baseline immunosuppression levels have been obtained.
- Randomized trials show either influenza high dose or booster dosing in same season has greater immunogenicity over a single standard dose and may be preferred over standard dosing.

References

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We are here to help!

VUMC Transplant Infectious Disease Group